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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/838,044

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Matthew R. Kaser

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INCYTE GENOMICS, INC.
3160 PORTER DRIVE
PALO ALTO, CA 94304

EXAMINER

LIU, SAMUEL W

ART UNIT

PAPER NUMBER

1653

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/838,044

Applicant(s)

KASER ET AL.

Examiner

Samuel W Liu

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 November 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above claim(s) 1-14, 17, 18 and 20-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15, 16 and 19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Applicants' response filed 13 November 2002 (paper No. 8) as to amendment of claim 15 has been entered. The following Office action is applicable to claims 15, 16 and 19.

The declaration filed on November 13, 2002 under 37 CFR 1.131 is sufficient to overcome Kikuno *et al.* reference.

Note that the grounds of objection and/or rejection not explicitly stated and/or set forth below are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 15, 16 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 (amended) recites "a protein selected from SEQ ID NOs:6-8"; the recitation is indefinite in that the claim includes non-elected SEQ ID NOs: 7 and 8 which are drawn to non-elected invention and thus renders the claim encompassing more one paternally distinct inventions. The dependent claims are also rejected.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Art Unit: 1653

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 15-16 and 19 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a well-established or disclosed specific and substantial credible utility.

The claimed protein is not supported by a specific asserted utility because the disclosed use of protein is generally applicable to screen a library of molecules, to purify a ligand from a sample (see page 4, the third paragraph) and thus is not particular the component of the pharmaceutical composition set forth in claim 9.

The specification sets forth use of the claimed protein (e.g., SEQ ID NO:6 polypeptide) for treating a disease state associated with the altered expression of gene in response to polycyclic aromatic hydrocarbon (PAH) exposure (see page 4, the second and the third paragraph). However, there is no example and guidance and no support as to how to make and use it in the specification regarding the claimed protein; the specification only provides evidence for human tissue expression at polynucleotide level NOT biologically active protein level. Thus, there is no specific utility and substantially utility associated with the claimed protein.

Also, the specification as filed does not disclose or provide any evidence that points to an activity (biological role or/and therapeutic role) of the protein. Additionally, there is no art of record that discloses or suggests any activity for the claimed protein. Thereof, there is no substantial utility.

The specification sets forth antibodies and the fragments thereof that bind the claimed protein for the diagnosis of disease state characterized by over-or-under expression of the protein

Art Unit: 1653

(see page 15, the forth paragraph). Such the recitation does not have positive input on the specific utility of the current disclosure because, at present, it has been widely accepted that the actual steady state level of mRNA molecules, is not well correlated with the actual protein abundance (see Aebersold, R. et al. (2000) *Annals of the New York Academy of Sciences* 919, 33-47), and because numerous proteins undergo *up* or *down* cellular regulation upon the extracellular signals, *e.g.*, toxic PHA compounds. Since the current application only provides working example and guidance as to the altered gene expression at polynucleotide level in response to PAH toxic compound, which is not necessarily and sufficiently for supporting that the expressed protein level is proportional to the expressed polynucleotide level thereof, there is no specific and sensational utility or well-established utility associated with the antibodies and fragments thereof. After further search, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of the invention and until it has been undertaken, applicants' claimed invention is incomplete. The current disclosure is therefore deemed lack of specific and substantial utility or well-established utility.

Claims 15-16 and 19 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention so that it would operate as intended without undue experimentation. This rejection stands for the reasons set forth in the foregoing statement of the grounds of rejection under 35 U.S.C. 101.

Applicant is not in possession of the claimed proteins and immunogenic fragments thereof for evidencing cytotoxicity or diagnosing the cytotoxicity associated disorder state in response to a PHA toxic compound. One of skill in the art would reasonably conclude that the disclosure insufficiently provides written description regarding the biological activity or role(s) of the claimed protein. The specification provide insufficient teaching, guidance, and no working examples as to make and use of the protein in evidencing cytotoxicity in the exposure to PHA compounds, and diagnosing or/and treating a disease state associated with the exposure thereof. Also, "an immunogenic fragment" (see claim 15) encompasses numerous polypeptide variants of the claimed protein (SEQ ID NO:6). One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of the variants to describe the immunogenic fragments. Thus, Applicant was not in possession of the pharmaceutical composition comprising the claimed protein and the claimed immunogenic fragment. *See University of California v. Eli Lilly and co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The current application is directed to a purified polypeptide that is used in a pharmaceutical composition in order to evaluating and identifying the environmental pollutants and the pollutant-mediated disease or disorder states. However, the specification does not provide working example, teaching, direction or guidance as to chromatographic purification of the protein as claimed and use of the purified protein as a pharmaceutical composition in order to

Art Unit: 1653

develop diagnostic and therapeutic agent for human condition, disease and disorders (see especially page 1, line 17-20, page 2, lines 29-32 and page 4, lines 22-25).

Claim 15 sets forth a substantially purified protein which is expressed in response to exposure to cytotoxic benzo(a)pyrene, and an immunogenic fragment thereof derived from the disclosed protein sequence. Yet, applicants provide no factual evidence regarding the substantially purified protein (SEQ ID NO:6) and the purified protein-mediated or the protein-directed uses in therapeutics and diagnosis. Applicants predict the functional uses of the claimed protein based on inspection of the presence of the polynucleotide that encodes the interest protein in response to exposure to the PHA compound.

The current disclosure sets forth an immunogenic fragment of the claimed protein. Yet, the specification provides no teachings, direction and working examples in regard to preparation of any fragments and testing for their immunogenicity. The instant claim language "a immunogenic fragment" includes a large quantity of subsequences, i.e., variants (the number of the variants is estimated at least 1.7×10^5). Such the recitation does not require that the corresponding polypeptide possesses the full-length sequence set forth in SEQ ID NO:6; but rather encompasses any subsequences or have *per se* been. Neither the specification provides any working examples of any subsequences. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:6 would be selected for uses in, e.g., screening a library of molecules (see page 13, lines 23-28), raising antibodies for diagnostic assay, and formulating with pharmaceutical carrier for prognosis, prevention, and treatment of the PHA pollutant-mediated diseases and complications (see page 13, lines 21-22).

The make and use of the immunogenic fragments are thus unpredictable for the reason set forth *supra*. The use of the fragments for immunodetecting full-length protein of SEQ ID NO:6 produced by cells is therefore highly unpredictable as well. Note that the folded full-length protein is immunogenically different from the unfolded oligopeptide (e.g., immunogenic fragments). Characteristics of the surface of a folded protein play an important role in antibody recognition. The amino acids may be widely separated in the linear structure of the protein but are close together when folded. The epitope recognition by an antibody are of two basic type 1) linear epitope that represent linear sequence of amino acids within oligopeptide or polypeptide, and 2) conformational epitopes in which the area recognized in the protein exists as a result of the 3-dimensional structure (i.e., folding structure) of the protein (see Miller, E. J. et al. *Am. J. Physiol.* (1991) 260, 1-12). Folding state and accessibility of antigen's idiotope to antibody are determining factors for affinity, specificity and valency with respect to antibody-antigen interaction.

The specification provides insufficient guidance as to (i) "conservative motif(s)" of the claimed protein for immunogenic recognition and (ii) applicability of fully folded, or partially folded, or unfolded protein including oligopeptide as a pharmaceutical composition. Since the claimed immunogenic fragments are structurally and functionally divergent in respect to their use in screening ligands and diagnosing and treating disorders associated with toxic compounds e.g., benzo(a)pyrene *etc.*, the specification needs to provide sufficient guidance to support enabling.

On the other aspect, since pollutant PAH compound not only induces multiple polynucleotide expression (see the foregoing statement) but also exerts its cellular pharmacological

Art Unit: 1653

effect through aryl hydrocarbon receptor/transcription factor (AhR) and induces apoptosis (see Shafat, A. *et al.* (2000) *Mol. Pharmacology*. 58, 515-525), these cellular characteristics of PHA would have an additionally unpredictable impact on the outcome of tissue expression profile as set forth in Table 1. In this regard, the specification needs also to provide sufficient guidance or direction to support the enablement.

In addition, the specification sets forth that "an agonist of the claimed protein may be administered to a subject to treat or prevent a disease associated with decreased expression or activity of the polypeptide" (see page 17, the fourth paragraph). There are no examples, however, provided in regard to this. The skilled artisan would not know to what the "agonist of the protein" refers. Until some actual and specific significance can be attributed to the protein identified in the specification as the protein SEQ ID NO: 6 or/and agonist of the protein and variants thereof, one of ordinary skill in the art would have been required to performed additional or/and undue experimentation in order to determine how to use the claimed invention. Thus, the claims are not fully enable for all variants, fragments, immunogenic fragments as presently claimed.

Description of invention's reduction to practice, unaccompanied by any meaningful, distinguishing characteristics of evolved the peptide variants, i.e., immunogenic fragments, is insufficient to satisfy written description requirement of 35 U.S.C. §112, since inventors could have provided description of claimed oligopeptide or portion of SEQ ID NO:6 protein, since actual reduction to practice may demonstrate possession of embodiment of invention, but it does not necessarily describe what invention is, and since, in context of present case, disclosure of manner in which invention was reduced to practice does not satisfy more fundamental written

description requirement set forth in Section 112.

In consideration of the issued stated *supra*, the amount and level of experimentation needed is undue.

Response to the rejection under 35 USC 112, the first paragraph

The response filed 13 November 2002 asserts that an immunogenic fragment of SEQ ID NO:6 is readily determined from the full-length sequence from which the fragments are derived; the derivation of fragments is described in Example VIII (see pages 10-11). The applicant's argument is unpersuasive for the reasons as follows. (i) Example VIII represents using software to identify suitable species of high immunogenicity; yet this is not adequately correlated to the claimed protein variants. The mediation of the immunogenic activity of the protein and fragments (variants) therefore does not establish actual reduction to practice. (ii) In order to satisfy the enablement requirement set forth in the first paragraph of 35 USC 112, identifying or/and characterizing a composition without teaching how to make and use the composition thereof is insufficient for enabling the disclosed composition (see also the forgoing the written description under the rejection of 35 USC 112, the first paragraph). (iii) The specification does not provide a representative working example or the related art in recorder in this regard so as to allow the stilled artisan to practice and use the claimed composition.

The response discusses the issue regarding use of the claimed protein and variants (i.e., the immunogenic fragments) thereof for therapeutic purpose based on over-or-under expression of the claimed protein (see pages 12-13). The applicant's argument has been fully considered but not persuasive. The claimed protein lacks specific substantial utility (see the corresponding

statement *supra*); thus, the antibodies against the protein and fragments thereof are deemed not enable. In view of the diagnosis of disease state characterized by over-or-under expression of the protein, the argument is unpersuasive as well. This is because (i) the said "over-or-under expression of the protein" does not have positive input on the specific and substantial utility of the current disclosure as there are numerous proteins being up- or down regulated upon the extracellular signals, e.g., toxic organic compound; and (ii) as yet, the actual steady state level of mRNA molecules is not well correlated with the actual protein abundance (see Aebersold, R. et al. (2000) *Annals of the New York Academy of Sciences* 919, 33-47). Thus, although the claimed polynucleotide is applicable for evidencing the PHA-induced cellular toxicity at polynucleotide level, the level of the protein and fragments encoded by the polynucleotide is necessarily proportional to the expressed polynucleotide level thereof (see also the corresponding statement *supra*). The disclosure needs to provide sufficient guidance or direction to support the enablement in this regard.

The response asserts that one skilled artisan would have a reasonable expectation that SEQ ID NO:6 expression level correlates with the levels of SEQ ID NO:1 mRNA (see pages 13-14). The applicant's argument is unpersuasive because of the reason set forth *supra*.

Further, the response discusses the issue regarding the immunogenic fragment which is based on Example VIII of the specification where describes use of software to identify a fragment having high immunogenicity, and infers that make and use of the immunogenic fragment des not require undue experimentation (see page 15, the second paragraph). The applicant's argument is unpersuasive because of the reasons set forth in the enablement rejection

Art Unit: 1653

under 35 USC 112, the first paragraph. Note that the recitation "an immunogenic fragment" encompasses numerous species, *i.e.*, variants of SEQ ID NO:6 protein fragments.

Response to the rejection under 35 USC 102 and 103

In light of the declaration filed on November 13, 2002 under 37 CFR 1.131 that is considered sufficient to overcome Kikuno *et al.* reference, the previous rejection under 35 USC 102 and 35 USC 103(a) are withdrawn.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.



Samuel Wei Liu, Ph.D.



KAREN COCHRANE CARLSON, PH.D.
PRIMARY EXAMINER

February 14, 2003